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APPLICATION NUMBER:

206099Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	January 26, 2016
From	Nicholas A. Kozauer, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	206,099
Supp #	
Proprietary / Established (USAN) names	Onzetra XSAIL (sumatriptan succinate)
Dosage forms / strength	22 mg delivered by the intranasal route
Proposed Indication(s)	Treatment of acute migraine with or without aura in adults
Recommended:	Approval

1. Introduction to Review

This application consists of a Class II resubmission submitted by Avanir Pharmaceuticals in response to a November 26, 2014 Complete Response letter for a new intranasal (powder) formulation of sumatriptan (Onzetra), to be administered by a breath powered delivery device (XSAIL). The Complete Response action was taken based on concerns that subjects could not correctly and safely self-administer the product as revealed by the results of a human factor (HF) submitted as part of the application.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Onzetra is a drug-device combination product intended for self-administration. The drug delivery system consists of a reusable breath powered device body incorporating a flexible mouthpiece device and a disposable pre-filled nosepiece that contains encapsulated sumatriptan succinate nasal powder (15.4 mg of sumatriptan succinate, equivalent to 11 mg sumatriptan base). A full dose of Onzetra is to be administered by use of two nosepieces (one used in each nostril). The drug-filled capsule is not removable from the nosepiece. For commercial distribution, the kit will contain two device bodies (b) (4) (b) (4) with (b) (4) (b) (4) nosepieces (two per pouch).

The original application for Onzetra was submitted on January 27, 2014. Please refer to the individual discipline reviews as well as Dr. Eric Basting's Division Director memo for the specifics of the issues raised during that review cycle. As noted above, the application was unable to be approved because of concerns raised by the Division of Medication Prevention and Analysis (DMEPA) reviewer related to the results of a HF study. To address these deficiencies, the applicant has subsequently reanalyzed the results of the HF and made changes to the product Instructions for Use (IFU) and package labeling intended to mitigate these

errors. These adaptations were then tested in a new summative HF validation study (Study AVA.2015.BRZ.502).

The application had also initially updated the application to withdraw the (b) (4) (b) (4) proposed commercial manufacturing and testing site, and to add UPM Pharmaceuticals (Bristol, Tennessee) as a proposed drug product manufacturing and testing site for AVP-825 finished drug product.

3. CMC/Microbiology/Device

Dr. Martha Heimann was the CMC reviewer for this application. As noted above, and as described in Dr. Heimann's review, when the applicant resubmitted the NDA on May 26, 2015, it withdrew (b) (4) as a manufacturing site and submitted a new contract manufacturer, UPM Pharmaceuticals, Bristol, Tennessee (UPM). However, following an August 14, 2015 inspection, the District Office initially classified the UPM facility as potential official action indicated (pOAI) and made a Withhold recommendation. Thus, the OPQ review dated October 10, 2015 recommended that the Agency issue a second CR letter.

Dr. Heimann's review goes on to note that on October 21, 2015, the applicant amended the NDA to reinstate (b) (4) as a drug product manufacturing site. This was classified as a major amendment, due to the need to reassess the (b) (4) facility status, and the PDUFA goal date was extended from November 6, 2015 to February 6, 2016. Subsequently, the Agency has determined that that status of (b) (4) remains acceptable. Dr. Heimann further states that during the review clock extension triggered by the amendment that reinstated the (b) (4) facility, the CDER Office of Compliance completed their review of the UPM inspection observations, and UPM's responses. Based on that review, the status of UPM was reclassified from pOAI to voluntary action indicated (VAI) and the Withhold recommendation revised to Acceptable. An overall Acceptable facility recommendation was entered on January 26, 2016.

As all other quality-related issues were resolved during the first review cycle for this application, and given the successful resolution of the manufacturing issues described above, Dr. Heimann recommends that the current application can be approved.

4. Nonclinical Pharmacology/Toxicology

Not applicable

5. Clinical Pharmacology/Biopharmaceutics

Not applicable

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical

The November 26, 2014 Complete Response letter noted that of the 27 subjects enrolled in the original HF study submitted with the initial application, only 14 were able to successfully administer a full treatment dose. A variety of errors (e.g., administering the dose to only one nostril, failing to administer any treatment for a number of reasons) were detailed. The concern was also raised that the HF study did not assess the ability of patients to ascertain whether or not the piercing process was successful through visualization alone. The letter recommended that the applicant further evaluate the root cause(s) of the failures seen in the HF study and implement additional mitigations to address the noted failures and concerns. Specifically, the letter requested that the applicant conduct an updated use-related risk analysis, and validate all user interface changes (including labeling, IFU, training, and/or device) in another human factors validation study with at least fifteen (15) representative users, to demonstrate that the changes are effective and that they do not introduce any new risks.

The current application provides a detailed description of the iterative review process that was used to revise the labeling for Onzetra. These changes included mitigations such as the streamlining of the information, the improvement of the clarity of the text and graphics, and the highlighting of critical steps more prone to errors in the Instructions for Use (IFU). Additionally, the applicant made two modifications to the proposed IFU related to capsule piercing. The applicant then conducted a new summative HF validation study which evaluated 15 participants who were clinically diagnosed as having acute migraines and who were currently on a prescription medication treatment regimen for migraines. Participants were not trained but were provided a self-familiarization period to review the materials, including the IFU and device, on their own if they wished, but they were not required to. The participants were then observed completing all tasks in the IFU independently for two doses separated by a distracter break.

The DMEPA reviewer for this application is Justine Harris, RPh. Dr. Harris has concluded that the results of the new HF summative study are acceptable. Specifically, Dr. Harris notes that 14 out of the 15 subjects carried out two successful dose simulations while 1 user delivered a partial dose during the first simulation and a full dose during the second simulation, corresponding to 29 out of 30 successful dose administrations. Additional details of the study results, including 5 “close calls”, are provided in her review.

DMEPA had also proposed additional revisions to the IFU, product labeling, and instructional video for Onzetra to further clarify and simplify the use of the product.

7. Advisory Committee Meeting

Not applicable

8. Other Relevant Regulatory Issues

Not applicable

9. Financial Disclosure

Not applicable

10. Labeling

The proposed labeling for this product largely mirrors the approved labeling for the currently marketed sumatriptan products, with additional data from the applicant's completed efficacy trial. Labeling negotiations around several non-substantive points took place during the review cycle, with a final agreement being reached between the Division and the applicant. Importantly, DMEP has agreed to the revised IFU and product labeling proposed by the applicant which was designed to mitigate the patient-use errors observed during the first human factors.

11. DSI Audits

Not applicable

12. Conclusions and Recommendations

I am recommending approval based on the resolution of the product use deficiencies outlined in the November 26, 2014 Complete Response letter as well as the resolution of the manufacturing site inspection concerns.

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/s/

NICHOLAS A KOZAUER
01/26/2016